

We claim:

1. An isolated siRNA comprising a sense RNA strand and an antisense
5 RNA strand, wherein the sense and an antisense RNA strands form an RNA duplex,
and wherein the sense RNA strand comprises a nucleotide sequence substantially
identical to a target sequence of about 19 to about 25 contiguous nucleotides in human
HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof.
- 10 2. The siRNA of claim 1, wherein the human HIF-1 alpha mRNA is SEQ
ID NO: 1.
3. The siRNA of claim 1, wherein the cognate of the human HIF-1 alpha
15 mRNA sequence is rat HIF-1 alpha mRNA or mouse HIF-1 alpha mRNA.
4. The siRNA of claim 1, wherein the sense RNA strand comprises one
RNA molecule, and the antisense RNA strand comprises one RNA molecule.
5. The siRNA of claim 1, wherein the sense and antisense RNA strands
20 forming the RNA duplex are covalently linked by a single-stranded hairpin.
6. The siRNA of claim 1, wherein the siRNA further comprises non-
nucleotide material.
- 25 7. The siRNA of claim 1, wherein the siRNA further comprises an
addition, deletion, substitution or alteration of one or more nucleotides.
8. The siRNA of claim 1, wherein the sense and antisense RNA strands
are stabilized against nuclease degradation.
- 30 9. The siRNA of claim 1, further comprising a 3' overhang.

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10. The siRNA of claim 9, wherein the 3' overhang comprises from 1 to about 6 nucleotides.

11. The siRNA of claim 9, wherein the 3' overhang comprises about 2
5 nucleotides.

12. The siRNA of claim 5, wherein the sense RNA strand comprises a first 3' overhang, and the antisense RNA strand comprises a second 3' overhang.

10 13. The siRNA of claim 12, wherein the first and second 3' overhangs separately comprise from 1 to about 6 nucleotides.

14. The siRNA of claim 13, wherein the first 3' overhang comprises a dinucleotide and the second 3' overhang comprises a dinucleotide.
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15. The siRNA of claim 14, where the dinucleotide comprising the first and second 3' overhangs is dithymidylic acid (TT) or diuridylic acid (uu).

16. The siRNA of claim 9, wherein the 3' overhang is stabilized against
20 nuclease degradation.

17. A retinal pigment epithelial cell comprising the siRNA of claim 1.

18. A recombinant plasmid comprising nucleic acid sequences for
25 expressing an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and an antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence of about 19 to about 25 contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof.

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19. The recombinant plasmid of claim 18, wherein the nucleic acid sequences for expressing the siRNA comprise an inducible or regulatable promoter.

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20. The recombinant plasmid of claim 18, wherein the nucleic acid sequences for expressing the siRNA comprise a sense RNA strand coding sequence in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter, and an antisense RNA strand coding sequence in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter.

21. The recombinant plasmid of claim 20, wherein the plasmid is pAAVsiRNA.

22. A recombinant viral vector comprising nucleic acid sequences for expressing an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and an antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence of about 19 to about 25 contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof.

23. The recombinant viral vector of claim 22, wherein the nucleic acid sequences for expressing the siRNA comprise an inducible or regulatable promoter.

24. The recombinant viral vector of claim 22, wherein the nucleic acid sequences for expressing the siRNA comprise a sense RNA strand coding sequence in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter, and an antisense RNA strand coding sequence in operable connection with a polyT termination sequence under the control of a human U6 RNA promoter.

25. The recombinant viral vector of claim 22, wherein the recombinant viral vector is selected from the group consisting of an adenoviral vector, an adeno-associated viral vector, a lentiviral vector, a retroviral vector, and a herpes virus vector.

26. The recombinant viral vector of claim 22, wherein the recombinant viral vector is pseudotyped with surface proteins from vesicular stomatitis virus, rabies virus, Ebola virus, or Mokola virus.

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27. The recombinant viral vector of claim 25, wherein the recombinant viral vector comprises an adeno-associated viral vector.

28. A pharmaceutical composition comprising an siRNA and a
10 pharmaceutically acceptable carrier, wherein the siRNA comprises a sense RNA strand and an antisense RNA strand, wherein the sense and an antisense RNA strands form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence of about 19 to about 25 contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form,
15 mutant or cognate thereof.

29. The pharmaceutical composition of claim 28, further comprising lipofectin, lipofectamine, cellfectin, polycations, or liposomes.

20 30. A pharmaceutical composition comprising the plasmid of claim 18, or a physiologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, further comprising lipofectin, lipofectamine, cellfectin, polycations, or liposomes.
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32. A pharmaceutical composition comprising the viral vector of claim 22 and a pharmaceutically acceptable carrier.

33. A method of inhibiting expression of human HIF-1 alpha mRNA, or an
30 alternative splice form, mutant or cognate thereof, comprising administering to a subject an effective amount of an siRNA comprising a sense RNA strand and an antisense RNA strand, wherein the sense and an antisense RNA strands form an RNA

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duplex, and wherein the sense RNA strand comprises a nucleotide sequence substantially identical to a target sequence of about 19 to about 25 contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof, such that human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof, is degraded.

34. The method of claim 33, wherein the subject is a human being.

35. The method of claim 33, wherein expression of human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof is inhibited in one or both eyes of the subject.

36. The method of claim 33, wherein expression of human HIF-1 alpha mRNA, or an alternative splice form, mutant or cognate thereof is inhibited in retinal pigment epithelial cells of the subject.

37. The method of claim 33, wherein the effective amount of the siRNA is an amount which provides an intercellular concentration at or near the neovascularization site of from about 1 nM to about 100 nM.

38. The method of claim 33, wherein the siRNA is administered in conjunction with a delivery reagent.

39. The method of claim 38, wherein the delivery agent is selected from the group consisting of lipofectin, lipofectamine, cellfectin, polycations, and liposomes.

40. The method of claim 39, wherein the delivery agent is a liposome.

41. The method claim 40, wherein the liposome comprises a ligand which targets the liposome to cells at or near the site of angiogenesis.

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42. The method of claim 41, wherein the ligand binds to receptors on tumor cells or vascular endothelial cells.

43. The method of claim 42, wherein the ligand comprises a monoclonal
5 antibody.

44. The method of claim 40, wherein the liposome is modified with an opsonization-inhibition moiety.

10 45. The method of claim 44, wherein the opsonization-inhibiting moiety comprises a PEG, PPG, or derivatives thereof.

46. The method of claim 33, wherein the siRNA is expressed from a recombinant plasmid
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47. The method of claim 33, wherein the siRNA is expressed from a recombinant viral vector.

48. The method of claim 47, wherein the recombinant viral vector
20 comprises an adenoviral vector, an adeno-associated viral vector, a lentiviral vector, a retroviral vector, or a herpes virus vector.

49. The method of claim 48, wherein the recombinant viral vector is pseudotyped with surface proteins from vesicular stomatitis virus, rabies virus, Ebola
25 virus, or Mokola virus.

50. The method of claim 47, wherein the recombinant viral vector comprises an adeno-associated viral vector.

30 51. The method of claim 33, wherein the siRNA is administered by an enteral administration route.

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52. The method of claim 51, wherein the enteral administration route is selected from the group consisting of oral, rectal, and intranasal.

53. The method of claim 33, wherein the siRNA is administered by a
5 parenteral administration route.

54. The method of claim 53, wherein the parenteral administration route is selected from the group consisting of intravascular administration, peri- and intra-tissue administration, subcutaneous injection or deposition, subcutaneous infusion,
10 intraocular administration, and direct application at or near the site of neovascularization.

55. The method of claim 54, wherein the intravascular administration is selected from the group consisting of intravenous bolus injection, intravenous
15 infusion, intra-arterial bolus injection, intra-arterial infusion and catheter instillation into the vasculature.

56. The method of claim 54, wherein the peri- and intra-tissue injection comprises peri-tumoral injection or intra-tumoral injection.
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57. The method of claim 54, wherein the intraocular administration comprises intravitreal, intraretinal, subretinal, subtenon, peri- and retro-orbital, trans-corneal or trans-scleral administration.

58. The method of claim 54, wherein the direct application at or near the site of neovascularization comprises application by catheter, corneal pellet, eye
25 dropper, suppository, an implant comprising a porous material, an implant comprising a non-porous material, or an implant comprising a gelatinous material.

59. The method of claim 54, wherein the site of neovascularization is in
30 the eye, and the direct application at or near the site of neovascularization comprises application by an ocular implant.

60. The method of claim 59, wherein the ocular implant is biodegradable.

61. A method of inhibiting angiogenesis in a subject, comprising
5 administering to a subject an effective amount of an siRNA comprising a sense RNA
strand and an antisense RNA strand, wherein the sense and an antisense RNA strands
form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide
sequence substantially identical to a target sequence of about 19 to about 25
contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form,
10 mutant or cognate thereof.

62. The method of claim 61, wherein the angiogenesis is pathogenic.

63. The method of claim 61, wherein the angiogenesis is non-pathogenic.
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64. The method of claim 63, wherein the non-pathogenic angiogenesis is
associated with production of fatty tissues or cholesterol production.

65. The method of claim 63, wherein the non-pathogenic angiogenesis
20 comprises endometrial neovascularization.

66. The method of claim 61, wherein the angiogenesis is inhibited in one
or both eyes of the subject.

25 67. A method of treating an angiogenic disease in a subject, comprising
administering to a subject an effective amount of an siRNA comprising a sense RNA
strand and an antisense RNA strand, wherein the sense and an antisense RNA strands
form an RNA duplex, and wherein the sense RNA strand comprises a nucleotide
sequence substantially identical to a target sequence of about 19 to about 25
30 contiguous nucleotides in human HIF-1 alpha mRNA, or an alternative splice form,
mutant or cognate thereof, such that angiogenesis associated with the angiogenic
disease is inhibited.

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68. The method of claim 67, wherein the angiogenic disease comprises a tumor associated with a cancer.

5 69. The method of claim 68, wherein the cancer is selected from the group consisting of breast cancer, lung cancer, head and neck cancer, brain cancer, abdominal cancer, colon cancer, colorectal cancer, esophagus cancer, gastrointestinal cancer, glioma, liver cancer, tongue cancer, neuroblastoma, osteosarcoma, ovarian cancer, pancreatic cancer, prostate cancer, retinoblastoma, Wilm's tumor, multiple
10 myeloma, skin cancer, lymphoma, and blood cancer.

70. The method of claim 67, wherein the angiogenic disease is selected from the group consisting of diabetic retinopathy, age-related macular degeneration, and inflammatory diseases.

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71. The method of claim 70, wherein the inflammatory disease is psoriasis or rheumatoid arthritis.

72. The method of claim 70, wherein the angiogenic disease is age-related
20 macular degeneration.

73. The method of claim 67, wherein the siRNA is administered in combination with a pharmaceutical agent for treating the angiogenic disease, which pharmaceutical agent is different from the siRNA.

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74. The method of claim 73, wherein the angiogenic disease is cancer, and the pharmaceutical agent comprises a chemotherapeutic agent.

75. The method of claim 73, wherein the chemotherapeutic agent is
30 selected from the group consisting of cisplatin, carboplatin, cyclophosphamide, 5-fluorouracil, adriamycin, daunorubicin, and tamoxifen.

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76. The method of claim 67, wherein the siRNA is administered to a subject in combination with another therapeutic method designed to treat the angiogenic disease.

- 5 77. The method of claim 76, wherein the angiogenic disease is cancer, and the siRNA is administered in combination with radiation therapy, chemotherapy or surgery.